

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
22 January 2004 (22.01.2004)

PCT

(10) International Publication Number
WO 2004/007497 A1

(51) International Patent Classification⁷: C07D 473/32 // (74) Agents: LEE, Ju-Ki et al.; 3rd Floor, Ducksung Bldg,
C07C 31:28, C01G 15/00 636-16 Yeoksam-dong, Kangnam-ku, Seoul 135-908 (KR).

(21) International Application Number:
PCT/KR2003/001396

(22) International Filing Date: 15 July 2003 (15.07.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10-2002-0041267 15 July 2002 (15.07.2002) KR

(71) Applicant (for all designated States except US):
KYUNG DONG PHARM. CO., LTD. [KR/KR]; 535-3,
Daeyang-ri, Yanggam-myun, Whaseong-si, Kyunggi-do
445-931 (KR).

(72) Inventors; and

(75) Inventors/Applicants (for US only): LEE, Byoung-Suk
[KR/KR]; 1-1106, Imgwang Apt., 1015 Bangbae3-dong,
Seocho-gu, Seoul 137-755 (KR). SHIN, Sang-Hoon
[KR/KR]; 308-402 Jugong APT., Byeolyang-dong,
Gwacheon-si, Kyeonggi-do 427-040 (KR).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK,
LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX,
MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD,
SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG,
US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR PREPARING 9-[4-ACETOXY-3-(ACETOXYMETHYL)BUT-1-YL]-2-AMINOPURINE

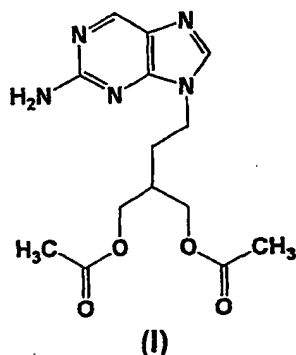
(57) Abstract: Disclosed is a process for preparing 9-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-aminopurine (called Famciclovir),
a drug of purine derivatives having antiviral activity. This process comprises reacting 2-aminopurine with 2-acetoxymethyl-4-bro-
mobut-1-yl-acetate in the presence of thallium (I) ethoxide to give the desired compound. According to this process, the desired
compound can be prepared in very high selectivity and purity under mild reaction conditions.

WO 2004/007497 A1

PROCESS FOR PREPARING 9-[4-ACETOXY-3-(ACETOXYMETHYL)BUT-1-YL]-2-AMINOPURINE

Technical Field

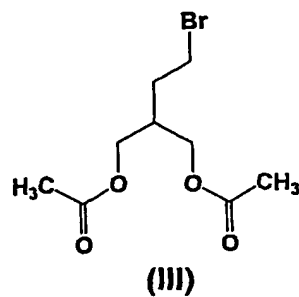
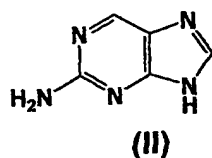
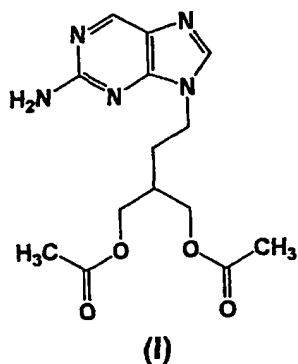
5 The present invention relates to a process for preparing 9-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-aminopurine (called Famciclovir) of Formula (I), a drug of purine derivatives having antiviral activity:



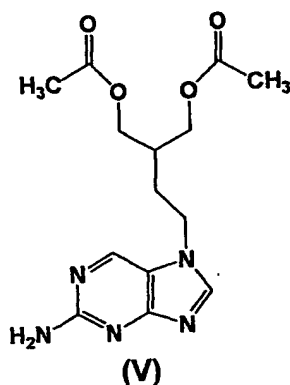
10 More particularly, the present invention relates to a novel process for preparing 9-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-aminopurine (called Famciclovir) of Formula (I), a drug of purine derivatives having antiviral activity, in which 2-aminopurine of Formula (II) is reacted with 2-acetoxymethyl-4-bromobut-1-yl-acetate of Formula (III) in the presence of thallium (I) ethoxide to give the compound of Formula (I) in high selectivity while minimizing the production of 7-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-aminopurine of Formula (V), a reaction byproduct:

15

20



TIOEt
(IV)

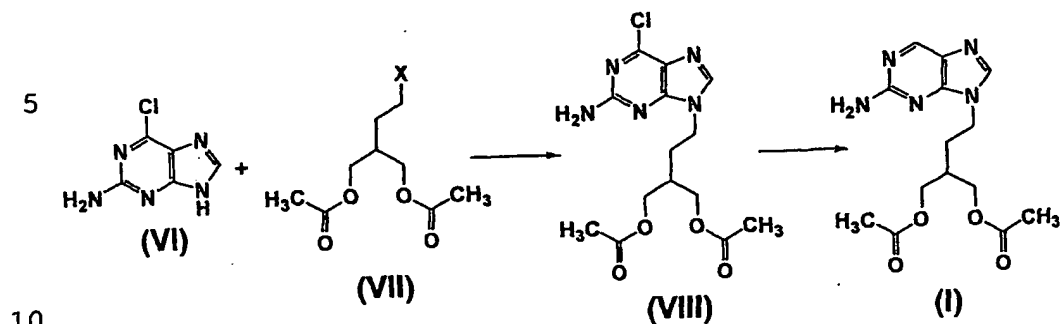


Background Art

Prior techniques for preparing the compound of
 5 Formula (I) are disclosed in European Patent No.
 182,024, and US Patent Nos. 5,684,153, 5,138,057 and
 5,917,041.

Among the above prior patents, EP No. 182,024 and
 US Patent No. 5,684,153 discloses a process for
 10 preparing 9-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-
 aminopurine of Formula (I), in which 2-amino-6-
 chloropurine of Formula (VI) is reacted with 2-
 acetoxymethyl-4-halobut-1-yl-acetate of Formula (VII) to
 give 9-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-amino-6-
 15 chloropurine of Formula (VIII), which is then reduced
 into the compound of Formula (I) in the presence of
 palladium, as shown in Scheme 1 below.

Scheme 1:

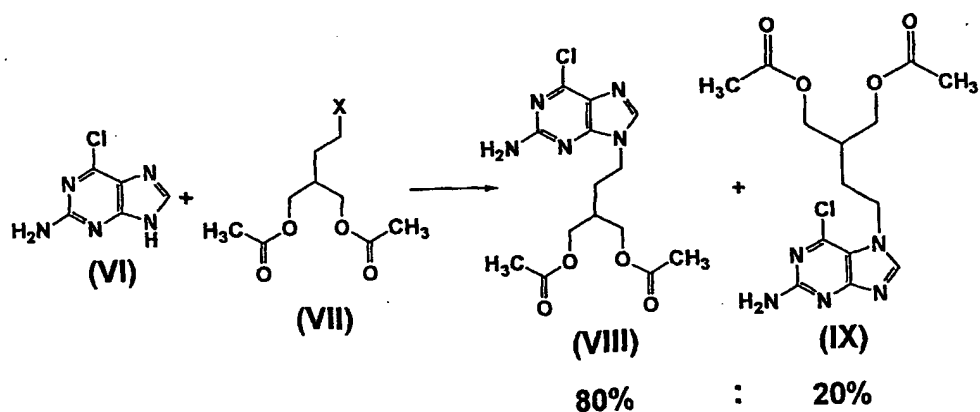


wherein X is a halogen atom.

However, the prior process according to Scheme 1 has problems in that the compound of Formula (VIII) and 7-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-amino-6-chloropurine of Formula (IX) as a byproduct are produced from the compound of Formula (VI) and the compound of Formula (VII) at a ratio of 80%:20%, as shown in Scheme 2 below, so that selectivity for the compound of Formula (VIII) is low and the purification of the compound of Formula (VIII) is very difficult.

20

Scheme 2:

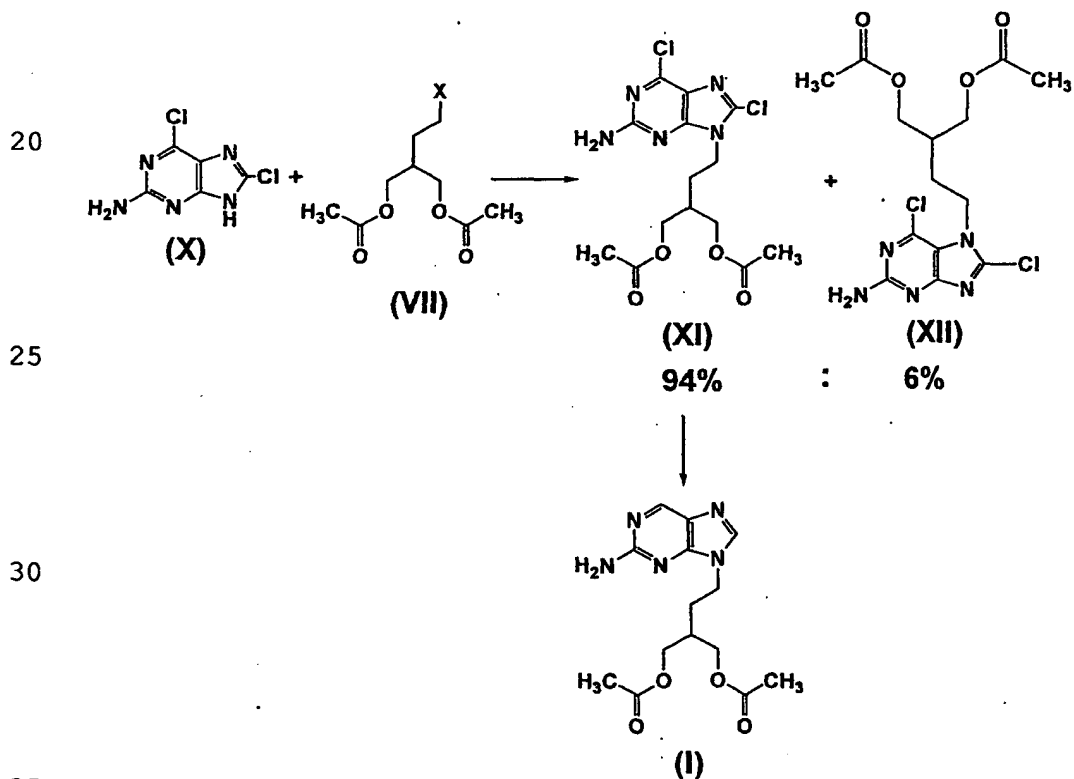


wherein X is a halogen atom.

Furthermore, the process according to Scheme 1 above has problems in that it requires the use of highly explosive palladium in the preparation of the compound of Formula (I) as the desired compound from the compound of Formula (VIII), and thus, is inefficient and unsuitable for industrial application.

Moreover, US Patent No. 5,138,057 discloses a process for preparing 9-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-aminopurine of Formula (I), in which 2-amino-6,8-dichloropurine of Formula (X) is reacted with 2-acetoxymethyl-4-halobut-1-yl-acetate of Formula (VII) to give 9-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-amino-6,8-dichloropurine of Formula (XI) which is then reduced under a pressurized condition in the presence of palladium, as shown in Scheme 3 below.

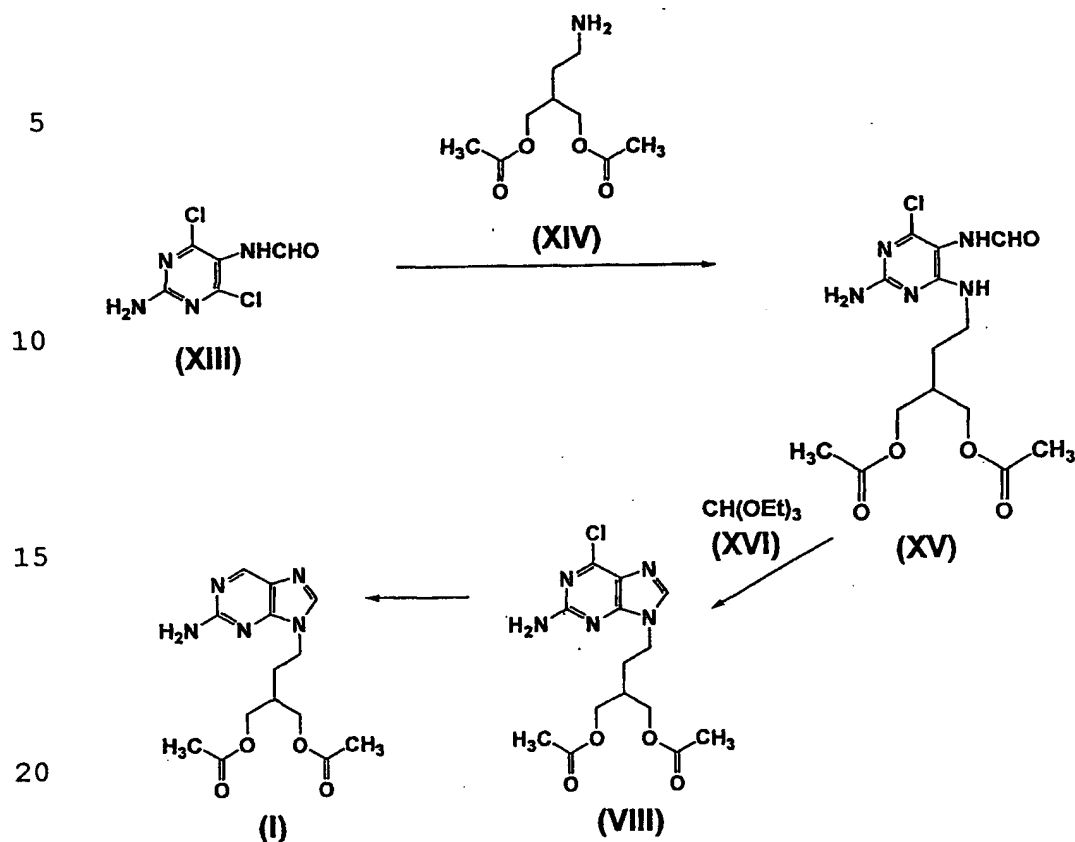
Scheme 3:



However, the process according to Scheme 3 shows relatively high selectivity for the compound of Formula (XI), since the compound of Formula (XI) and 7-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-amino-6,8-dichloropurine of Formula (XII) as a reaction byproduct are produced from the compound of Formula (X) and the compound of Formula (VII) at a ratio of 94%:6%. However, this process has problems in that it requires the use of highly explosive palladium in the production of the compound of Formula (I) as the desired product from the compound of Formula (XI), as in EP No. 182,024 and US Patent No. 5,684,153, and needs to be carried out under a pressurized condition higher than 50 psi, thus posing difficulty in industrial application.

In addition, US Patent No. 5,917,041 discloses a process for preparing 9-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-aminourine of Formula (I), in which N-(2-amino-4,6-dichloro-5-pyrimidinyl)formamide of Formula (XIII) is reacted with 2-acetoxymethyl-4-aminobut-1-yl-acetate of Formula (XIV) to give a compound of Formula (XV) which is then converted into 9-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-amino-6-chloropurine of Formula (VIII) by means of triethylorthoformate of Formula (XVI), and then the compound of Formula (VIII) is reduced into the compound of Formula (I) in the presence of palladium, as shown in Scheme 4 below.

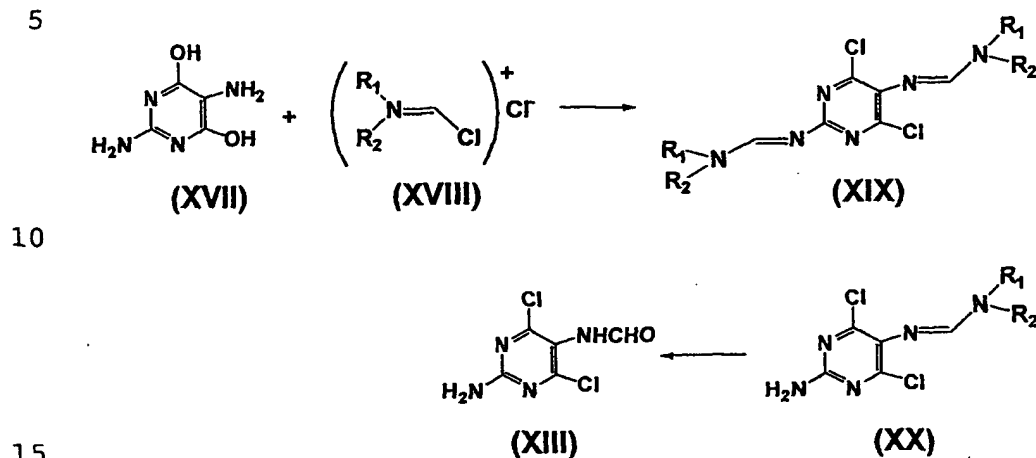
Scheme 4:



However, the process according to Scheme 4 has
 25 problems in that it requires the use of expensive 2,5-
 diamino-4,6-dihydroxypyrimidine of Formula (XVII) and
 expensive chloromethylene iminium salt of Formula
 (XVIII) in the production of the compound of Formula
 (XIII) as a starting material, as shown in Scheme 5
 30 below, and gives the compound of Formula (I) as the
 desired product at a very low yield of about 32% via
 several steps from the compound of Formula (XVII), and
 also requires the use of highly explosive palladium as
 in EP No. 182,024 and US Patent No. 5,684,153 as
 35 described above, so that it utilizes a long reaction

route and is inefficient and thus has a difficulty in industrial application.

Scheme 5:



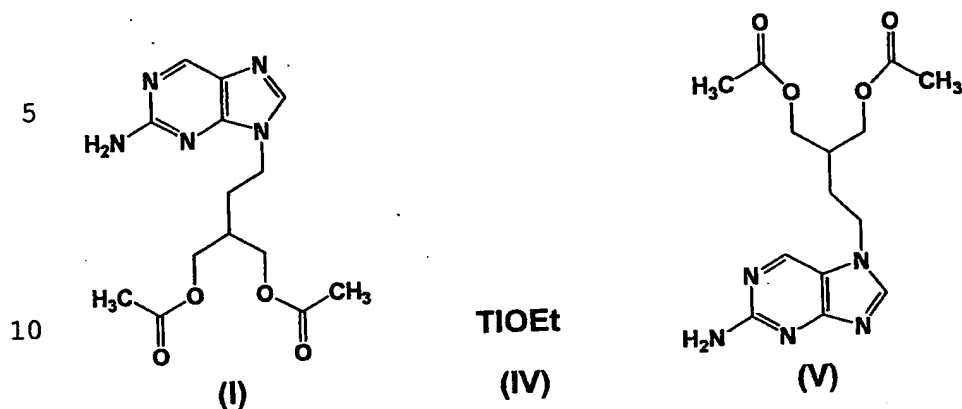
Thus, in the relevant field of art, there has been demanded the development of a process which allows the preparation of 9-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-aminopurine (called Famciclovir), a drug of purine derivatives having antiviral activity, at high selectivity under mild reaction conditions, while minimizing the production of 7-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-aminopurine as a reaction byproduct.

Disclosure of the Invention

According to a preparing process of the present invention, owing to the introduction of thallium (I) ethoxide critical to this process, 9-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-aminopurine (called Famciclovir) of Formula (I), a drug of purine derivatives having antiviral activity, can be prepared in a very high selectivity of 98% while minimizing the production of 7-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-

8

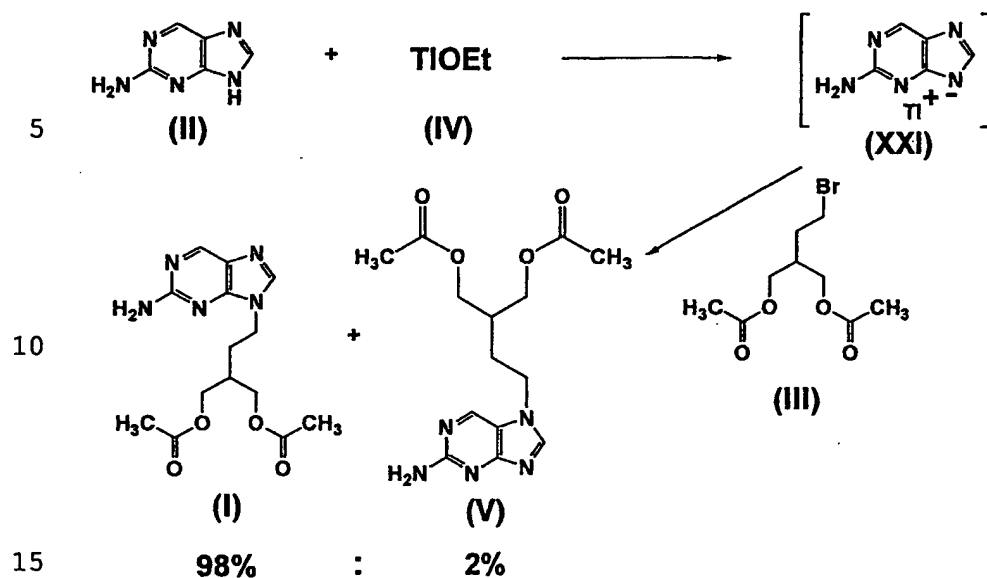
aminopurine of Formula (V) as a reaction byproduct:



15 More specifically, according to the process of the present invention as shown in Scheme 6 below, 2-aminopurine of Formula (II) is reacted with thallium (I) ethoxide of Formula (IV) in polar organic solvent at about 0-100 °C, and preferably about 10-30 °C, for about 20 2-50 hours, and preferably about 20-40 hours, to give 2-aminopurine-thallium salt of Formula (XXI) as an intermediate. Then, the compound of Formula (XXI) is reacted with 2-acetoxy-4-bromobut-1-yl-acetate of Formula (III) in polar organic solvent at about 0-100 °C, 25 and preferably about 10-30 °C, for about 50-200 hours, and preferably about 70-100 hours, to give Famciclovir of Formula (I) as the desired compound. Moreover, according to the process of the present invention, since Famciclovir of Formula (I) and 7-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-aminopurine of Formula (V) as 30 a reaction product are produced at a ratio of 98%:2%, the desired compound can be prepared in very high selectivity.

35

Scheme 6:



The compound of Formula (II), which is used as the starting material in the process of the present invention, is commercially available or can be produced according to methods described in, for example, *Heterocycles*, 17, 405 (1982) and *Journal of the Chemistry Society*, 2060 (1954). Also, the compound of Formula (III), a branched hydrocarbon, which is used as the starting material in the process of the present invention, can be prepared according to the conventional method, such a method described in European Patent Publication No. 141,927.

Preferred examples of the polar organic solvent, which can be used in the preparing process of the present invention, include N,N-dimethylformamide, dimethylsulfoxide, lower alcoholic solvents with 1-3 atoms, such as methanol, ethanol and isopropanol, and a mixture thereof.

Best Mode for Carrying Out the Invention

The present invention will hereinafter be described in further detail by examples. It should however be borne in mind that the present invention is not limited to or by the examples.

5

Example 1: Preparation of 2-aminopurine, thallium salt

6.75 g (50 mmole) of 2-aminopurine was suspended in 140 ml of anhydrous ethanol, and the temperature of a reactor was maintained below 15 °C. The suspension was added slowly with 18.72 g (75 mmole) of thallium (I) ethoxide, followed by stirring for 36 hours at room temperature. At the end of the reaction, the stirred mixture was filtered, and washed with anhydrous ethanol to give 15.57 g (92%) of 2-aminopurine-thallium salt.

15 Melting point: 290-292 °C (dec.)

IR: ν_{\max} (cm^{-1}): 3400, 3180, 3060, 2800, 1650, 1580, 1512, 1421

¹H NMR (DMSO- d_6 , 300MHz) (ppm):

6.35 (2H, brs, -NH₂)

20 8.13 (1H, s, H of C-8)

8.65 (1H, s, H of C-6)

Example 2: Preparation of 9-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-aminopurine

16.92 g (50 mmole) of 2-aminopurine-thallium salt was suspended in 140 ml of N,N-dimethylformamide, and the temperature of a reactor was maintained below 15 °C. The suspension was added slowly with a solution of 16.03 g (60 mmole) of 2-acetoxymethyl-4-bromobut-1-yl-acetate in 30 ml of N,N-dimethylformamide, followed by stirring for 84 hours at room temperature. At the end of the reaction, the stirred mixture was cooled and filtered, and then the filtrate was concentrated under reduced pressure to evaporate the solvent. The residue was purified by silica gel chromatography (CHCl₃:MeOH=90:1)

11

to give 9.80 g (61%) of 9-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-aminopurine ($R_f=0.82$).

Melting point: 101-103 °C (dec.)

IR: ν_{\max} (cm^{-1}): 3330, 3163, 1746, 1729, 1654, 1612, 1582

5 ^1H NMR ($\text{DMSO}-d_6$, 300MHz) (ppm):

1.99-1.95 (3H, m, $=\text{NCH}_2\text{CH}_2\text{CH}=\text{}$)

2.00 (6H, s, $-\text{CH}(\text{CH}_2\text{OCOCH}_3)_2$)

4.03 (4H, d, $-\text{CH}(\text{CH}_2\text{OCOCH}_3)_2$)

4.14 (2H, t, $=\text{NCH}_2\text{CH}_2\text{CH}=\text{}$)

10 6.45 (2H, brs, $-\text{NH}_2$)

8.09 (1H, s, H of C-8)

8.57 (1H, s, H of C-6)

Also, 0.19 g (1.2%) of 7-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-aminopurine as a reaction byproduct was obtained ($R_f=0.49$).

Melting point: 137-139 °C

IR : $\nu_{\max}(\text{cm}^{-1})$: 3330, 3160, 1743, 1728, 1645, 1606

^1H NMR ($\text{DMSO}-d_6$, 300MHz) (ppm) :

20 1.86-2.03 (9H, m, $=\text{NCH}_2\text{CH}_2\text{CH}=\text{}$ and $-\text{CH}(\text{CH}_2\text{OCOCH}_3)_2$)

4.07 (4H, d, $-\text{CH}(\text{CH}_2\text{OCOCH}_3)_2$)

4.16 (2H, t, $=\text{NCH}_2\text{CH}_2\text{CH}=\text{}$)

6.38 (2H, brs, $-\text{NH}_2$)

8.06 (1H, s, H of C-8)

25 8.61 (1H, s, H of C-6)

Example 3: Preparation of 9-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-aminopurine

16.92 g (50 mmole) of 2-aminopurine-thallium salt was suspended in 140 ml of N,N-dimethylformamide, and the temperature of a reactor was maintained below 15 °C. The suspension was added slowly with a solution of 16.03 g (60 mmole) of 2-acetoxymethyl-4-bromobut-1-yl-acetate in 30 ml of N,N-dimethylformamide, followed by stirring for 84 hours at room temperature. At the end of the

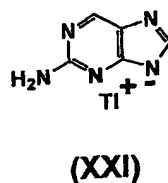
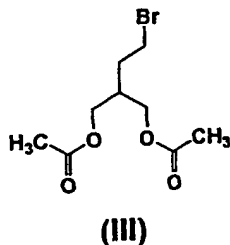
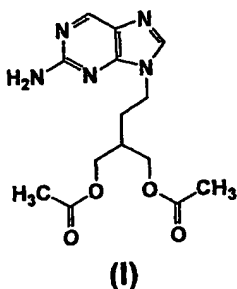
- reaction, the stirred mixture was cooled and filtered, and then the filtrate was added with 100 ml of water. The solution was extracted three times with 70 ml of CHCl_3 , and dried over magnesium sulfate, and then
- 5 concentrated under reduced pressure to evaporate the solvent. The residue was crystallized from a mixed solvent of ethyl acetate, hexane and tert-butanol, to give 8.35 g (52%) of 9-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-aminopurine.
- 10 Spectrum data analyzed for the compound obtained in Example 3 were identical to Example 2.

Industrial Applicability

- As can be seen from the foregoing, according to
- 15 the process of the present invention, 9-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-aminopurine (called Famciclovir) of Formula (I), a drug of purine derivatives having antiviral activity, can be prepared in a very high selectivity under mild reaction
- 20 conditions while minimizing the production of 7-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-aminopurine of Formula (V) as a reaction byproduct.

Claims

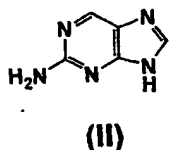
1. A process for preparing a compound of Formula (I), which comprises reacting a compound of Formula (XXI) with a compound of Formula (III) in a polar organic solvent:



2. The process of Claim 1, wherein the polar organic solvent is at least one selected from the group consisting of N,N-dimethylformamide, dimethylsulfoxide, lower alcoholic solvents with 1-3 carbon atoms, and a mixture thereof.

3. The process of Claim 1 or 2, wherein the reaction is carried out at a temperature of 0-100 °C.

4. The process of Claim 1, wherein the compound of Formula (XXI) is obtained by the reaction of a compound of Formula (II) with a compound of Formula (IV):



5. The process of Claim 4, wherein the reaction is carried out in at least one polar organic solvent selected from the group consisting of N,N-dimethylformamide, dimethylsulfoxide, lower alcoholic

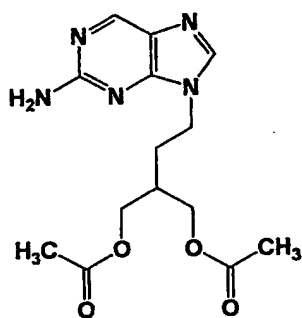
14

solvents with 1-3 carbon atoms, and a mixture thereof.

6. The process of Claim 4 or 5, wherein the reaction is carried out at a temperature of 0-100 °C.

5

7. Use of thallium (I) ethoxide (TIOEt) for the preparation of 9-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-aminopurine of Formula (I):



(I)

10

15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 03/01396-0

CLASSIFICATION OF SUBJECT MATTER

IPC⁷: C07D 473/32 // C07C 31/28, C01G 15/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC⁷: C07D, C07C, C01G

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

—

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

REGISTRY, CASREACT, EPO, WPI, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4020073 A (E. C. TAYLOR et al.) 26 April 1977 (26.04.77) <i>column 3, line 41 - column 4 line 13, claims, examples 18,19.</i>	1-7
A	US 3626018 A (E. C. TAYLOR) 7 December 1971 (07.12.71) <i>column 3, lines 5- 39, examples 18,19, claims.</i>	1-7
A	GB 1205373 A (E. C. TAYLOR et al.) 16 September 1970 (16.09.70) <i>page 1, page 3 lines 4-56, examples 14,15, claims.</i>	1-7
	—	

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

„A“ document defining the general state of the art which is not considered to be of particular relevance

„E“ earlier application or patent but published on or after the international filing date

„L“ document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

„O“ document referring to an oral disclosure, use, exhibition or other means

„P“ document published prior to the international filing date but later than the priority date claimed

„T“ later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

„X“ document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

„Y“ document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

„&“ document member of the same patent family

Date of the actual completion of the international search

26 September 2003 (26.09.2003)

Date of mailing of the international search report

20 October 2003 (20.10.2003)

Name and mailing address of the ISA/AT

Austrian Patent Office

Dresdner Straße 87, A-1200 Vienna

Facsimile No. 1/53424/535

Authorized officer

WENIGER S.

Telephone No. 1/53424/341

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR 03/01396-0

Patent document cited in search report			Publication date	Patent family member(s)	Publication date
GB	A	1205373		none	
US	A	3626018		none	
US	A	4020073		none	